REMARKS

Applicants thank the Examiner for her careful consideration of the present application and of cited references 1-35. However, Applicants note that the Examiner has not initialed references 36-94 to indicate that they have been considered during the examination of this application. Applicants respectfully request the consideration of these references. In the event that the Examiner considers these citations not to be in conformance, Applicants respectfully request the Examiner to inform Applicants of the reasons therefore and means to present these references in a manner which would allow their consideration.

The amendments to the claims find support in the specification and claims as filed. The amendments to claims 18, 19, 36, 43, 46, 47, and 48 delete the trademarked term HERCEPTIN®. The amendments to claim 26 remove reference to a Figure, correct a typographical error, and insert the chemical structure of Figure 3. Support for the insertion of the chemical structure is found in the specification, for example, at page 7, lines 10-14. No new matter is added by way of the amendments.

Claims 1, 2, 4-6, and 8-48 are pending in the application. Claims 14-16, 18, 19, 35, 36, 43, and 46-48 stand rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was allegedly not set forth in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Claims 18, 19, 36, 43, 47 and 48 stand rejected under 35 U.S.C. § 112, second paragraph as indefinite. Claims 1, 2, 4-6, 8-17, 20-35, and 37-42 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chari (U.S. 6,436,931) in view of Hudziak (U.S. 5,725,856). Claims 1, 34 and 37 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chari (U.S. 6,436,931) in view of Hudziak (U.S. 5,725,856) in view of Kasprzyk (Cancer Res. 52:2771-2776 (1992)). Claim 26 stands objected to for referring to a figure.

The Rejections Under 35 U.S.C. § 112, first paragraph

Claims 14-16, 18, 19, 35, 36, 43, and 46-48 stand rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was allegedly not set forth in the specification in such as way as to enable one skilled in the art to make and/or use the invention. In particular, the Examiner noted that claims 14-16, 18, 19, 35, 36, 43, and 46-48 are drawn to methods using the specifically named monoclonal antibodies 4D5, 2C4, humanized 4D5, and humanized 2C4.

Applicants respectfully note that monoclonal antibodies 4D5 and 2C4 are on deposit with the American Type Culture Collection (ATCC) as was noted in the specification as originally filed. For example, the ATCC accession number for cell line 4D5 was noted on page 6, line 17 and elsewhere in the specification. The ATCC accession number for cell line 2C4 was noted on page 4, lines 4-5 and on page 10, lines 4-5, for example. Humanized antibodies were noted, for example, on page 10, lines 7-12, which includes incorporation by reference of U.S. Patent 5,821,337 disclosing huMAb4D5-8 (commercially available as HERCEPTIN®). Humanized 2C4 antibodies and their sequences are disclosed in Figs. 1 and 2 of the specification.

Applicants further respectfully draw the Examiner's attention to the published application, which includes notice of the deposit of this biological material at paragraphs 282-288, immediately preceding the Sequence Listing. This section states, in part:

"The following hybridoma cell lines have been deposited with the American Type Culture Collection, 10801 University Boulevard, Manassas, Va. 20110-2209, USA (ATCC):

2 Antibody Designation ATCC No. Deposit Date 7C2 ATCC HB-12215 October 17, 1996 7F3 ATCC HB-12216 October 17, 1996 4D5 ATCC CRL 10463 May 24, 1990 2C4 ATCC HB-12697 April 8, 1999

[0284] This deposit was made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of viable cultures for 30 years from the date of the deposit. The organisms will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the cultures to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 USC .sctn.122 and the Commissioner's rules pursuant thereto (including 37 CFR .sctn.1.12 with particular reference to 886 OG 638).

[0285] In respect of those designations in which a European patent is sought, a sample of the

deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample. (Rule 28(4) EPC)

[0286] The assignee of the present application has agreed that if the cultures on deposit should die or be lost or destroyed when cultivated under suitable conditions, they will be promptly replaced on notification with a viable specimen of the same culture. Availability of the deposited strain is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws."

Thus, Applicants respectfully submit that the specification provides sufficient disclosure so that one of skill in the art can produce or obtain the specifically named monoclonal antibodies 4D5, 2C4, humanized 4D5 and humanized 2C4. Accordingly, Applicants respectfully submit that the rejections to claims 14-16, 18, 19, 35, 36, 43, and 46-48 under 35 U.S.C. § 112, first paragraph are overcome.

The Rejections Under 35 U.S.C. § 112, second paragraph

Claims 18, 19, 36, 43, 47 and 48 stand rejected under 35 U.S.C. § 112, second paragraph as indefinite for including the trademark HERCEPTIN®.

As amended, claims 18, 19, 36, 43, 47 and 48 recite the humanized monoclonal antibody huMAb4D5-8 and do not refer to it by the trademarked name HERCEPTIN®. Accordingly, Applicants believe that these claims are not indefinite, and respectfully submit that the rejections to claims 18, 19, 36, 43, 47 and 48 under 35 U.S.C. § 112, second paragraph are overcome.

The Rejections to claims 1, 2, 4-6, 8-17, 20-35, and 37-42 under 35 U.S.C. § 103(a)

Claims 1, 2, 4-6, 8-17, 20-35, and 37-42 stand rejected under 35 U.S.C. § 103(a) as obvious over Chari (U.S. 6,436,931) in view of Hudziak (U.S. 5,725,856). Chari is presented by the Examiner as providing antibody conjugates to maytansinoid and methods of use. Hudziak is presented by the Examiner to provide an anti-ErbB2 antibody that is a growth inhibitory antibody. Applicants respectfully submit that claims 1, 2, 4-6, 8-17, 20-35, and 37-42 are not obvious under 35 U.S.C. § 103(a) over the cited references.

"In order to establish a prima facie case of obviousness, there must be 1) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on the applicant's disclosure." In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Claim 1 recites, in part, "A method for the treatment of a tumor in a mammal, wherein the tumor is characterized by the overexpression of an ErbB2 receptor and does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody ...." Thus, the treatment methods of claim 1 and its dependent claims 2, 4-6, 8-17, 20-35, and 37-42 are directed to *in vivo* treatment of mammalian tumors that 1) overexpress an ErbB2 receptor, and 2) do not respond, or respond poorly, to treatment with an anti-ErbB2 antibody.

Neither of the cited references discusses treating a mammalian tumor characterized by the overexpression of an ErbB2 receptor that does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody. Neither of the cited references discusses or provides treatment for such a tumor. Such treatments are not found in the general knowledge of one of ordinary skill in the art. Thus, the cited references, even if considered in combination with the knowledge of one of ordinary skill in the art, fail to provide at least these elements of the claimed invention.

Moreover, there is no suggestion in either of the cited references to treat such a tumor, nor any suggestion of methods directed to treating such a tumor, nor any suggestion or motivation to combine the cited references together to provide such a method of treatment. Lacking any discussion of such treatments, and lacking any suggestion of such treatments, the cited references also fail to provide any reasonable expectation of success for such treatments.

Accordingly, since the cited references do not disclose a method for treating a mammalian tumor characterized by the overexpression of an ErbB2 receptor that does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody, provide no motivation to combine the cited references to provide the claimed invention, nor any reasonable expectation of success were the references to be so combined, applicants respectfully submit that claims 1, 2, 4-6, 8-17, 20-35, and 37-42 are not made obvious by Chari in view of Hudziak.

The Rejections to claims 1, 34 and 37 under 35 U.S.C. § 103(a)

Claims 1, 34, and 37 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chari in view of Hudziak and further in view of Kasprzyk (Cancer Res. 52:2771-2776 (1992)). Chari and Hudziak are presented by the Examiner as discussed above. Kasprzyk is applied by the Examiner as presenting the use of combinations of anti-ErbB2 antibodies in the treatment of gastric cancer.

As discussed above, Chari and Hudziak fail to discuss or suggest treatment for a tumor that overexpresses an ErbB2 receptor and does not respond, or responds poorly, treatment with an anti-ErbB2 antibody. Kasprzyk similarly fails to discuss or suggest treatment of such a tumor. Applicants thus respectfully submit that Chari and Hudziak and Kasprzyk together fail to provide all the elements of the claimed invention. Moreover, these references also fail to provide suggestion or motivation to combine their teachings to provide the claimed invention, for at least the reason that none of these references discusses tumors having characteristics as recited in claims 1, 34 and 37.

Accordingly, since the cited references do not disclose a method for treating a mammalian tumor characterized by the overexpression of an ErbB2 receptor that does not respond, or responds poorly, to treatment with an anti-ErbB2 antibody, provide no motivation to combine the cited references to provide the claimed invention, nor any reasonable expectation of success were the references to be so combined, applicants respectfully submit that claims 1, 34, and 37 are not made obvious by Chari in view of Hudziak in view of Kasprzyk.

The Objection to Claim 26

Claim 26 stands objected to for referring to Figure 1. As amended, claim 26 now recites SEQ ID NO:1, and does not recite Fig. 1. Accordingly, Applicants respectfully submit that the objection to Claim 26 is overcome.

CONCLUSION

Applicants respectfully submit that claims 1, 2, 4-6, and 8-48 stand in allowable form, and respectfully request their reconsideration and allowance. Early notification of the allowance of all claims is respectfully requested.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641.

Respectfully submitted,

Dated: February 24, 2003

By: _____
James A. Fox
Registration No. 38,455

Heller, Ehrman White & McAuliffe
275 Middlefield Road
Menlo Park, California 94025-3506
(650) 324-6951 telephone
(650) 324-6654 facsimile

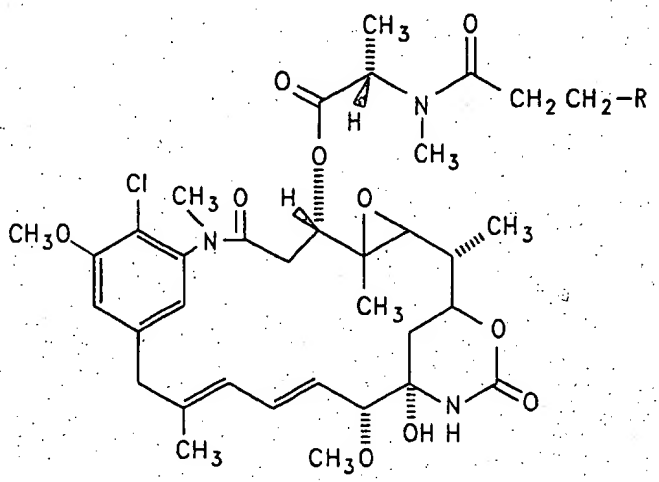
Marked-Up Copy of the Changes Made

In the Claims

18. (Amended) The method of claim 17 wherein the antibody is selected from the group consisting of humanized antibodies huMAb4D5-1, huMAb4D5-2, huMAb4D5-3, huMAb4D5-4, huMAb4D5-5, huMAb4D5-6, huMAb4D5-7 and huMAb4D5-8 [(HERCEPTIN®)].

19. (Amended) The method of claim 18 wherein the antibody is humanized antibody huMAb4D5-8 [(HERCEPTIN®)].

26. (Amended) The method of claim 25 wherein the [maytansioid] maytansinoid is DM1 [shown in Figure 1] having the structure



36. (Amended) The method of claim 34 wherein the second antibody is humanized antibody, huMAb4D5-8 [(HERCEPTIN®)].

43. (Amended) The method of claim 42 wherein the unconjugated antibody is humanized antibody huMAb4D5-8 [(HERCEPTIN®)] or humanized 2C4.

46. (Twice Amended) The method of claim 1 wherein said treatment has an improved objective response rate compared to treatment with huMAb4D5-8 [(HERCEPTIN®)] alone.

47. (Twice Amended) The method of claim 1 wherein said treatment has a longer duration of response than treatment with huMAb4D5-8 [(HERCEPTIN®)] alone.

48. (Twice Amended) The method of claim 1 wherein said treatment results in increased survival of the mammal treated compared with treatment with huMAb4D5-8 [(HERCEPTIN®)] alone.